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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,590	11/25/2003	Dennis Triglia	VITA1120-1	7574

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,590	TRIGLIA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-29* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22, 24, 25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-24-07 has been entered.

Applicants' amendment filed 4-24-07 and the declaration filed 3-2-07 have been entered. Claims 20-22 have been amended. Claim 23 has been canceled. Claims 1-22 and 24-29 are pending. Claims 20-22, 24, 25 and 29 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 20-22, 24, 25 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "hollow fiber is formed from a material which has a pore size of about 0.1 um to 0.3 um" in the newly amended claims 20, 21 and 22 is considered new subject matter. The only support in the specification is on page 19, lines 23-25, which states "the membrane has

pores from about 0.1 um to about 0.3 um in diameter". The specification discloses "the **membrane** has pores from about 0.1 um to about 0.3 um **in diameter**", rather than "**a material** which has a **pore size of about 0.1 um to 0.3 um**". The specification fails to provide sufficient support for the phrase set forth above. Therefore, the phrase "hollow fiber is formed from a material which has a pore size of about 0.1 um to 0.3 um" in the newly amended claims 20, 21 and 22 is considered new subject matter. Claims 24, 25 and 29 depend from claim 22.

4. Claims 20-22, 24, 25 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an extracorporeal bio-artificial liver device comprising an apparatus containing cells of the cell line deposited as ATCC accession No. CRL-12461 cultured in serum-free medium on a surface of the device for expressing albubinalpha-1-antitrypsin, factor V, complement C3 and antithrombin III etc., wherein the surface is contained within a hollow fiber cartridge, does not reasonably provide enablement for the extracorporeal bio-artificial device set forth above, wherein the device provides liver specific biological activity at a level sufficient to sustain a subject having a liver disorder or compromised liver function, a method of using the cells to provide bio-artificial liver support for the subject, and a method of treating a subject having compromised liver function, such as Fulminant hepatic failure (FHF). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 20-22, 24, 25 and 29 are directed to an extracorporeal bio-artificial liver device comprising an apparatus containing cells of the cell line deposited as ATCC accession No. CRL-12461, wherein the cells have a doubling time in serum-free medium which is less than about

70% of the doubling time in serum-free medium for C3A cells, cultured in serum-free medium on a surface of the device in an amount to provide liver specific biological activity sufficient to sustain a subject having a liver disorder or compromised liver function, and wherein the surface is contained within a hollow fiber cartridge having a pore size about 0.1 um to 0.3 um, a method of using the cells of the cell line CRL-12461 to provide bio-artificial liver support for the subject, and a method of treating a subject having compromised liver function, such as FHF. Claim 25 specifies the subject is a human. Claim 29 specifies the protein is albumin.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification discloses the establishment of a clonal C3A cell line 2.5B1 cultured in serum-free medium and has less than 70% of doubling time of the parent C3A cell line, detection of gluconeogenesis, glycogen synthesis and the synthesis of antichymotrypsin, antitrypsin, antithrombin III, complement C3, factor V and transferrin in said cell line. Claims 20-25

encompass using any cell line, derived from parent C3A cell line, cultured in serum-free medium with doubling time significantly less than the doubling time of parent C3A cell line for treating a subject having compromised liver function.

The specification encompasses culturing clonal C3A cells, i.e. cells of ATCC accession No. CRL-12461, on various type of extracorporeal bio-artificial device made of different materials and designs to treat numerous different liver disorders or diseases in a subject with said device. The specification fails to provide adequate guidance and evidence for whether the clonal C3A cell line, having doubling time less than 70% of that of parental C3A cells in SFM, can be cultured in or on any bio-artificial device to produce sufficient clonal C3A cells in SFM so as to provide sufficient liver specific biological activity for removal of blood-borne molecules in the blood of a subject having compromised liver function and to treat said subject with said device. Strain et al., 2002 (Science, Vol. 295, p. 1005-1009) reports a bioartificial liver (BAL) must provide a number of crucial liver functions including synthesizing many proteins, such as clotting factors, producing bile, regulating carbohydrate, fat and protein metabolism, detoxifying ammonia product and breaking down alcohol and drugs. "The problem is deciding which liver functions are the most important and should be carried out by the BAL bioreactor" (middle column, p. 1005). Strain points out that primary hepatocyte loses liver-specific gene expression and become phenotypically unstable in culture and non-parenchymal liver cells and bile duct epithelial cells are important for optimal hepatic activity, and "[t]he enormous scale-up required to use BAL devices clinically is problematic: At least 10^{10} hepatocytes in a BAL bioreactor would be needed to support a patient's failing liver (right column, p. 1005). The claims read on using the clonal C3A cells for treating a subject having compromised liver function alone. The

specification fails to provide adequate guidance and evidence whether the clonal C3A cells are phenotypically stable and can provide sufficient liver specific biological activities without the presence of non-parenchymal liver cells and bile duct epithelial cells for optimal hepatic activity as taught by Strain, and whether sufficient number of clonal C3A cells could be cultured on the BAL to support a patient's failing liver. Further, "[t]he ideal BAL design must ensure optimal ex vivo maintenance of hepatocytes. It has been assumed, but not yet proven, that simple "flow through" BAL systems achieve this. However, given that conventional monolayer cultures cannot optimally maintain hepatocytes, it is likely that hepatocytes will need to be induced to form cellular aggregates in which they reacquire their polarization (middle column, p. 1006). "The greatest challenge for the BAL bioreactor is how best to maintain viable functional hepatocytes outside of the body" and "[I]nteractions among the different types of hepatic cell populations are essential for the liver to operate appropriately. Coculture of hepatocytes with nonparenchemal liver cells has been shown to be beneficial (5). The downside is that inclusion of other cell types would inevitably make BAL design, construction, and handling even more complex" (right column, p. 1007). The specification fails to provide adequate guidance and evidence for whether the clonal C3A cells alone would form a monolayer of cells or form cellular aggregates in which type of BAL device, and whether the clonal C3A cells would be able to provide sufficient liver specific biological activities for treating a subject having compromised liver function.

Further, a subject having compromised liver function includes a subject having numerous different liver disease or disorders. Different liver diseases or disorders differ pathologically, morphologically and physiologically, and the mechanisms that result in compromised liver

function could vary dramatically in different liver diseases or disorders. The specification fails to provide adequate guidance for what would be the pathological symptoms for compromised liver function and whether the claimed extracorporeal bio-artificial liver device would be able to ameliorate those symptoms. The specification fails to provide adequate guidance for the correlation between removal of blood-borne molecule entering the device as well as release of molecules from the cells and treatment of a subject having compromised liver function. It is unclear what kind of blood-borne molecules should be removed from the blood entering the artificial device and what kind of molecules should be released from the cells into blood exiting said device so as to provide therapeutic effect for treating a subject having compromised liver function. It is also unclear whether sufficient clonal C3A cells can be cultured on or in the bio-artificial device and whether sufficient liver specific biological activity could be provided to recover the compromised liver function for treating a subject having compromised liver function. Absent the specific guidance, one skilled in the art at the time of the invention would not know how to use the recited clonal C3A cells (ATCC accession No. CRL-12461) on various types of bio-artificial device to treat numerous different liver disorders or diseases in a subject with said device.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the level of the ordinary skill which is high, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that the claims have been amended to recite extracorporeal bio-artificial device and specific dimension of the hollow fiber cartridge, and the declaration filed 3-2-07 demonstrates the biocompatibility, safety and efficaciousness of an extracorporeal liver assist device comprising the cells as claimed. Applicants further argue that the specification teaches critical liver functions that must be considered, polarization of the cells, dimension of the device, cell density to achieve necessary function and a specific disease to be treated, i.e. FHF (amendment, p. 7-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph and that the declaration fails to point out what cells have been used in the ELAD and whether the ELAD used is the same as the claimed extracorporeal bio-artificial liver device. The declaration also fails to disclose whether the ELAD is used before and/or after the transplantation. It appears that the ELAD was used before transplantation to serve as a bridge to transplantation. The ELAD increases the rate of recovery from sublethal acute liver failure of specific disease FHF and has the capacity to support patients for several days to serve as an effective bridge to transplantation. Therefore, the ELAD was used to provide liver support for FHF patient while they are waiting for liver transplantation rather than being used to treat FHF patient. It is unclear what would be the pathological symptoms of various liver diseases and disorders, and there is no evidence of record that show the ELAD ameliorates those symptoms in the patient.

Further, the specification only provides a prophetic method of treating a subject having a liver disorder by using a bio-artificial device. Bioartificial liver (BAL) must provide a number of crucial liver functions including synthesizing many proteins, such as clotting factors, producing bile, regulating carbohydrate, fat and protein metabolism, detoxifying ammonia product and

breaking down alcohol and drugs. It is unclear whether the claimed cells can provide those crucial liver functions and whether sufficient cells can be obtained in the bio-artificial liver device to provide therapeutic effect in a subject. The claims read on using the claimed cells for treating a subject having compromised liver function alone. The specification fails to provide adequate guidance and evidence whether the claimed cells are phenotypically stable and can provide sufficient liver specific biological activities without the presence of non-parenchymal liver cells and bile duct epithelial cells for optimal hepatic activity as taught by Strain, and whether sufficient number of claimed cells could be cultured on the BAL to support a patient's failing liver.

A subject having compromised liver function includes a subject having numerous different liver disease or disorders. Different liver diseases or disorders differ pathologically, morphologically and physiologically, and the mechanisms that result in compromised liver function could vary dramatically in different liver diseases or disorders. The specification fails to provide adequate guidance for the correlation between removal of blood-borne toxic solutes entering the device as well as release of molecules from the cells and the treatment of a subject having compromised liver function. It is unclear what kind of blood-borne toxic solutes should be removed from the blood entering the artificial device and what kind of molecules should be released from the cells into blood exiting said device so as to provide therapeutic effect for treating a subject having a particular liver disorder or compromised liver function.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER